REMARKS

Status of Claims and Amendment

Upon entry of this amendment, which is respectfully requested, claims 1, 2, and 15-17 will be amended. New claims 18-20 will be added. Claims 1-20 are all the pending claims in the application. Claims 10 and 12 are withdrawn as being drawn to a non-elected species. Claims 1-9, 11, and 13-17 are rejected.

Claim 1 has been amended to even more clearly recite that (1) the pharmacodynamics of a drug in step (a) is "determined based upon data obtained from *in vitro* studies of the effect of the drug in animal cells, and optionally *in vivo* studies in animals, and pharmacokinetics of the drug is determined based on data obtained from *in vivo* studies in animals", (2) in step (b), "the drug of (a) is administered to at least one human, and the phase I clinical trial is performed in parallel with performing computer simulations", (3) in step (c), "at least a single dose of step (b) is incrementally increased in at least one dose escalation step", and (4) in step (d), "calculation of the at least one dose escalation step by the computer simulations of the computer model in step (c) to obtain a maximal tolerated dose, a minimum effective dose, and a recommended dose." In addition, claim 1 has been amended to delete step (i). Support for the amendments to claim 1 may be found at least at paragraphs [0137]-[0161] and Figs. 5A-5L of the specification.

Claim 2 has been amended to delete "sub step".

Claims 15-17 have been amended to even further clarify that "the computer model is an in silico patient that interacts with the results" of the clinical trials. Support for the amendments

to claims 15-17 may be found at least at paragraphs [0138], [0146], and [0148] of the specification.

Support for new claims 18-20 may be found at least at paragraphs [0154]-[0164] and Figs. 5J-5M of the specification.

No new matter is added

Specification

Applicants thank the Examiner indicating acceptance of the substitute specification.

Claim Objections

Claims 1, 15 and 17 are objected to for the following informalities:

1) Claim 1 is objected for the recitation "performing phase II (or phase III or IV) clinical trial". The Examiner suggests grammatically correcting the claim to recite "performing phase II clinical trials or performing a phase II clinical trial".

2) Claims 15 and 17 are objected for the recitations "related studies, the comprising". The Examiner suggests amending the claim to recite "related studies, the method comprising".

With regard to claim 1, it appears the Examiner has misread the claim because there is no recitation of "performing phase II (or phase III or IV) clinical trial" to correct to the recitation suggested by the Examiner.

With regard to claims 15 and 17, Applicants have amended the claims as suggested by the Examiner.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite for the following reasons.

1. Claim 1 is asserted to be allegedly unclear because of the recitation "performing a pre-clinical phase in which a computer model for pharmacokinetics and pharmacodynamics of the drug is created and adjusted based on *in vitro* studies and *in vivo* studies". The Examiner appears to assert that it is unclear as to what *in vitro* or *in vivo* studies are utilized to create or adjust a model.

In response, Applicants note that one of ordinary skill in the art would understand from reading the specification, e.g., at paragraphs [0138]-[0148] and Figs. 5A-5E, that the pharmacodynamics (PD) of a drug is determined based upon data obtained from *in vitro* studies conducted on animal cells, e.g., human and rodent cells, and optionally data obtained from *in vivo* studies conducted in animals. Further, one of ordinary skill in the art would understand that the pharmacokinetics (PK) of a drug is determined based upon data obtained from *in vivo* studies conducted in animals. Specifically, validation and fine-tuning of the PK and PD model in humans in parallel with Phase I clinical trials is described in paragraphs [0146]-[0148] and Fig. 5E. Figs. 5A-5C describe the design of *in vitro* and *in vivo* experiments designed to produce a set of parameters required for the PK and PD models. The parameters are summarized in Fi. 5D.

Applicants note that both PK and PD models use information from *in vitro* and *in vivo* experiments. Information from animals is essential for PK modeling. However, additional information from *in vitro* studies may also be used, for example, information from plasma

protein binding assays, bioavailability assays, drug dissolution and interaction assays with hepatocytes, may be used.

PD models are usually based upon animal models, e.g., drug dose effect on the animal, but may include *in vitro* data, e.g., dose effect on cell viability.

Further, one of ordinary skill in the art would understand from reading the present specification, e.g., at paragraphs [0095] and [0109], the relation of PK and PD models to *in vitro* and *in vivo* models. In other words, a computer model for the PK and PD of a drug is created and adjusted based on *in vitro* studies in anima cells, and *in vivo* studies in animals. Figure 5D summarizes the parameters in the PK and PD models. For example, the *in vivo* variable, "$E_{Di(TT)}(r)$", defined in paragraph [0064] of the specification is directly related to the construction of the PD model.

As disclosed by Fridborg *et al.*[1], which is incorporated by reference into the present specification (see paragraph [0008] of the specification), "[t]he results demonstrate a significant relationship between toxicity *in vitro* and achievable systemic exposure of anticancer drugs in humans, which suggests that non-clonogenic *in vitro* assays for drug sensitivity testing may provide pharmacokinetic information useful in the development of investigational cytotoxic drugs."

[1] See also http://www.ncbi.nlm.nih.gov/pubmed/7756685?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

2. Claim 1 is asserted to be allegedly unclear because of the recitation "wherein the phase I clinical trail comprises a plurality of sub-steps". The Examiner asserts that it is unclear as to what sub-steps are involved.

In response, Applicants note that the claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, Applicants have deleted this phrase.

In addition, Applicants note that one of ordinary skill in the art would understand from reading the specification, e.g., at paragraph [0009] and Figs. 5E-5H, that the steps of a Phase I clinical trial involve *in vivo* administration of the safe starting dose determined from the pre-clinical studies of step (a) in step (b) in parallel with a computer simulation of the computer model in an In Situ Patient in which the dose is adjusted for the computer simulation based upon the results from the Phase I clinical trials in step (c) to obtain the maximal tolerated dose, minimal effective dose, and recommended dose determined in step (d), provided the results obtained from the clinical trial (CT) indicates that at least a single dose for the drug administered is more effective than a chosen threshold dose (X) for the drug administered.

3. Claim 1 is asserted to be allegedly unclear because of the recitation "determining maximal tolerated dose, minimum effective dose...in conjunction with the computer simulations". The Examiner appears to assert that it is unclear as to what computer simulations are in conjunction with the dose.

In response, Applicants note that the claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution

of the present application, Applicants have amended step (d) of claim 1 to even more clearly recite that the maximal tolerated dose, minimum effective dose, and recommended dose is calculated based upon the at least one dose escalation step by the computer simulations of the computer model in step (c).

As disclosed in paragraphs [0074], [0076], and [0087] of the specification, one of ordinary skill in the art would understand that computer simulations may calculate the minimal effective dose, maximal tolerated dose, and recommended dose. The computer simulations are conjugated to the clinical trials as described in paragraphs [0148]-[0151] and Figures 5E, 5F, 5G, and 5H. According to standard drug development in the pharmaceutical arts, the minimal effective dose, maximal tolerated dose, and recommended dose are evaluated at the end of an experimental procedure. These parameters are evaluated based on animal trials which replace the initial computer model parameters, and the model simulations provide improved values of the minimal effective dose, maximal tolerated dose, and recommended dose. The model is adjusted as long as the clinical trial continues, and the predictions become more precise. Running the model on a wide range of doses, exploring the simulation outcomes as to the efficacy and the toxicity of the treatment result in an improved indication of a regimen that should be further tested in humans. The predictive model provides a wide variety of regimens that efficiently determines the next experimental trial that should be done as well as the overall outcome of the trial.

4. Claim 1 is asserted to be allegedly unclear because of the recitation "analyzing interim results of step h, to choose the most promising regimens..."

In response, Applicants note that the claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, Applicants have amended 1 to delete step (i).

6. Claim 17 is asserted to be allegedly unclear because there is insufficient antecedent basis for the recitation "developing a strategy for a next sub-step in phase I clinical trial" when a "first sub-step" was not performed.

In response, Applicants note that the claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, Applicants have deleted "a next sub-step" in claim 17.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 102(b)

Claims 15-17 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Iliadis *et al.* for reasons of record. For brevity, these reasons are not reiterated below.

In addition, the Office Action asserts that Applicants' arguments that Iliadis is not applicable because Iliadis conducted no clinical trials is not persuasive because Applicants' claimed invention is drawn to performing computer simulations based on clinical trial data. The Office Action asserts that Iliadis anticipates models based upon computer simulations and data gathered from clinical trials.

Moreover, the Office Action states that Applicants' arguments were not persuasive because although "[t]he specification describes a design in which an "in silico" patient engine is

used for drug development on page 15...[h]owever, this is not what is claimed, nor is this described as defining the "interactive clinical trial." (see paragraph bridging page 10-11 of Office Action mailed April 19, 2007).

Applicants note that Iliadis does not anticipate the presently claimed invention because (1) the present invention involves performing clinical trials in parallel with computer simulations in an in silico patient to obtain data to predict drug efficacy, and toxicity in order to provide an optimal regime, and (2) the present invention requires assessment of data obtained from *in vitro* and or *in vivo* pre-clinical trials. In contrast, although Iliadis discloses a mathematical model to determine the efficacy and toxicity of a drug, such model is based upon obtaining clinical information after a clinical trial has been performed, and such model is not an interactive in silico patient.

Iliadis teaches a mathematical model for simulation of efficacy and toxicity of a cancer drug (ectoposide). For the configuration of this model, i.e., setting the model's parameters), Iliadis gathers clinical information from the literature of a typical patient, whereas some parameters were only assumed. For instance, "volume distribution, $V_1 = 25$ liters", "total clearance, CL = 50 liters * day $^{-1}$" (see page 217, paragraph 5 of Iliadis), the active drug concentration below which no tumor cells were killed, $C_{MIN} = 0.1\mu g * ml^{-1}$ (page 217, paragraph 7 of Iliadis), and physiological level of WBC count, $W_0 = 8 \text{ X } 10^9$ ((page 218, paragraph 1 of Iliadis).

However, the mathematical model of Iliadis is not based on preclinical studies of *in vitro* and *in vivo* in animals and therefore does not disclose the presently claimed invention of claim 15.

Also, the presently claimed invention of claim 16 requires a part of a Phase I clinical trial where dose escalation occurs. Claim 16 requires the use of a model to predict the outcomes of the treatment so that a Phase I clinical trial would be accomplished in a more efficient way. In particular, the dose escalation process is aided by the model simulations. In contrast, the model of Iliadis does not implement this aspect, i.e., the model of Iliadis does not relate to Phase I clinical trials and, in particular, to dose escalation.

Similarly, claim 17 requires the option to select the next clinical experiment that is to be performed, based upon the outcomes of the model simulations. Again, the Iliadis model does not require this step.

Further, as acknowledged by the Office Action, that the mathematical calculations of Iliadis is not performed in parallel with a clinical trial because Iliadis discloses "a first phase [that] relies on modeling to simulate the fate of drug concentration, tumor size, and WBC…[and a] second phase [that] involves protocol implementation, based on the model" (see page 5, 1st full paragraph of the Office Action).

Thus, Iliadis does not explicitly or inherently disclose the presently claimed method wherein the computer model is an interactive in silico patient.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

for

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1: Anticancer Drugs. 1995 Feb;6(1):64-9.

Links

Relationship between pharmacokinetic parameters in patients and cytotoxicity in vitro of standard and investigational anticancer drugs.

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The selection of the starting dose for initial clinical trials of anticancer agents is mostly determined by toxicological endpoints in mice (LD10). So far, very few attempts have been made to evaluate the potential value of cytotoxicity assays for this purpose. The present study was undertaken as a first attempt to investigate the relationship between cytotoxicity of anticancer drugs in vitro and pharmacokinetic parameters in vivo in patients, at suggested maximum tolerated doses. Using the fluorometric microculture cytotoxicity assay (FMCA), we determined the concentration giving 50% cell survival (IC50) in vitro, for 25 cytotoxic drugs in fresh preparations of normal peripheral blood mononuclear cells (PBMC) and of tumor cells from patients with acute or chronic lymphocytic leukemia (ALL or CLL). Using linear regression, we investigated the relationship between the IC50s and clinically achievable peak plasma concentrations (Cmax) or concentration-time products (C x T) in humans. The clinical data was obtained from the literature. Based on all drugs tested, good correlations were obtained between IC50s for CLL cells, and both Cmax and C x T (R approximately 0.7, $p < 0.0002$), and for ALL cells and normal PBMC between IC50 and Cmax, while the two latter cell types showed somewhat weaker relationships to C x T. Using the IC50 data of CLL cells, predictions of Cmax and C x T exceeded 1 log for only four drugs. No tendencies to under- or overprediction within different classes of drugs were noted. The results demonstrate a significant relationship between toxicity in vitro and achievable systemic exposure of anticancer drugs in humans, which suggests that non-clonogenic in vitro assays for drug sensitivity testing may provide pharmacokinetic information useful in the development of investigational cytotoxic drugs.

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